Med Sci Monit, 2001; 7(5): 995-1001

Incidence of Chlamydia pneumoniae infection in patients with coronary artery disease subjected to angioplasty or bypass surgery

Piotr Pieniążek[1], Elżbieta Karczewska[2], Ewa Stępień[3], Wiesława Tracz[1], Stanisław J. Konturek[2]

[1] Department of Cardiac and Vascular Disease, Collegium Medicum, Jagiellonian University, Cracow, Poland
[2] Department of Physiology, Collegium Medicum, Jagiellonian University, Cracow, Poland
[3] Laboratory, Department of Cardiac and Cardiovascular Surgery and Transplantology, Collegium Medicum, Jagiellonian University, Cracow, Poland

key words: coronary artery disease, atherosclerosis, Chlamydia pneumoniae, IgG, IgA, infection, revascularization

SUMMARY

Background: *Seroepidemiological, pathological and animal studies suggest that chronic infection with Chlamydia pneumoniae (Cp) may directly impact the development or progression of atherosclerosis and coronary heart disease. The aim of the present study was to determine the seroprevalence of Cp infection and markers of systemic inflammation in patients undergoing routine coronary artery examination and prior to heart revascularization.*

Material and methods: *The research involved 76 patients with severe CAD and 81 control patients with normal coronary circulation confirmed by coronary angiography. The presence of serum IgG and IgA antibodies to Cp and plasma interleukin-8 (IL-8) levels was measured by EIA test. Furthermore, the levels of plasma C-reactive protein, fibrinogen, total cholesterol, and triglycerides were measured in all patients.*

Results: *Seropositivity to Cp was found in 60.5% for IgG and in 61.8% of cases for IgA with CAD patients, as compared to 26.0% and 29.5% in the controls ($p<0.001$), respectively. The levels of Interleukin-8, plasma fibrinogen, total cholesterol and triglycerides were significantly higher ($p<0.001$) in the CAD group, while C-reactive protein tended to have a higher value in patients with atherosclerosis than in the control group, although the difference was not significant.*

Conclusions: *Cp infection significantly increases the risk of CAD, usually requiring coronary bypass surgery or percutaneous coronary intervention as effective measures. It may also modify the levels of serum lipids, CRP and fibrinogen, increasing the risk of atherosclerosis. The strong correlation between the elevated IgG and IgA titers of Cp in patients treated with angioplasty or surgery may impact their follow-up; this issue requires further investigation.*

BACKGROUND

Several studies recently reported an association between coronary heart disease and certain persistent bacterial and viral agents, including herpes viruses, cytomegalovirus, coxackie B4 virus, *Helicobacter pylori* (Hp) and *Chlamydia pneumoniae* [1–10]. *Chlamydia pneumoniae* (Cp) is an obligate, intracellular pathogen and a common cause of benign respiratory symptoms [11–15]. In most studies Cp is the third most common cause of pneumonia. Studies on antibody prevalence indicate a worldwide incidence of pneumonia, and in some countries even higher than 50% of the adult population [16]. Cp usually causes around 6–10% of cases of community-acquired pneumonia [17,18]. During epidemics it may account for up to 50% of such infections [19].

Received: 2001.06.21
Accepted: 2001.07.20

Correspondence address: Prof. Stanisław J. Konturek MD PhD, Department of Physiology, Collegium Medicum, Jagiellonian University, Grzegórzecka 16, 31-531 Kraków, Poland

Infection is predominantly linked with several chronic inflammatory conditions, especially coronary artery disease (CAD) and atherosclerosis. An association between chlamydial infection and vascular disease was first reported in 1988 [20]. The additional evidence that has accumulated since the late 1980s from seroepidemiological, pathological and animal studies suggests that Cp may directly impact the development or progression of atherosclerosis and CAD.

The association between Cp and atherosclerosis is based on evidence derived from the tissue examination of arterial plaque material [19], and has also been demonstrated in atherectomy specimens originating from patients with angina, and the atheromatous arteries of patients with other vascular diseases. In recent studies Cp has been detected using PCR (polymerase chain reaction) for the assessment of Cp genomic deoxyribonucleic acid (DNA) and immunocytochemistry, in a greater proportion of coronary atheromatous lesions, and less frequently in other tissues [20–22].

The presence of Cp within coronary atheroma suggests that this respiratory pathogen is probably conveyed from the lungs to the cardiac tissue before the infection of the cellular components of the coronary arteries occurs [23]. Monocytes and macrophages may carry the bacteria along from the respiratory tract to the coronary arteries. Subsequent direct endothelial damage caused by a chronic infection of the endothelium in a genetically predisposed individual may lead to the formation and progression of atherosclerotic lesions. Alternatively, the Cp-infected macrophages arriving at the already-formed plaque lesions may become activated and then perpetuate the various inflammatory and procoagulant processes essential to atherothrombosis. Subsequent plaque instability may lead to adverse cardiovascular events, e.g. acute coronary syndromes, or cardiac death.

The aim of the present study was to determine the seroprevalence of Cp infection (Cp antibodies IgG and IgA) and the presence of non-specific inflammation markers, such as proinflamatory cytokines (IL-8), as well as alterations in plasma C-reactive protein, fibrinogen, cholesterol and triglycerides in patients undergoing routine coronary angiography prior to being referred to percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

MATERIAL AND METHODS

Two groups of patients (A and B) were studied. Group A consisted of 76 patients with coronary artery disease (CAD), median age 54 years, age range from 40 to 68, admitted to the Department of Cardiac and Vascular Diseases. Their condition was evaluated using clinical history, physical examination, EKG, maximum stress test, and cardiac coronary angiography according to the Judkins technique. Group B consisted of 81 controls, matched by age, gender, and socioeconomic status, who were also examined in the same way in the Cardiology Unit, but had negative cardiac angiography; CAD was ruled out in all of them as well. None of the controls had previously suffered a myocardial infraction. All of them produced negative stress test results, although they were diagnosed with various types of arrhythmia, hypertension, or chest discomfort with normal coronary arteries.

Coronary artery disease in the Group A patients, confirmed angiographically, was diagnosed whenever at least 70% stenosis was encountered in one or more coronary arteries, or at least 50% stenosis in the left main coronary artery. Previous myocardial infarction was recognized in 31 patients (40%), unstable angina in 15 patients (20%), and hypertension in 48 patients (63%). Percutaneous coronary intervention, including stent implantation and directional atherectomy (DCA), was carried out in 48 patients (63%); 23 patients (30%), however, were referred for CABG. Five patients were disqualified from PCI or CABG due to multiple coronary lesions, or the small dimensions of the coronary vessels.

Maximum stress test

Exercise on the treadmill combined with electrocardiography (exercise stress testing) is important in the diagnosis of angina pectoris. The purpose of this exercise stress testing is to document the EKG, blood pressure and symptomatic response to a gradual increase in exercise, with constant EKG and blood pressure monitoring for as long as the patient can tolerate this exercise. The stress test exercise procedure is stopped at a predetermined heart rate, typically 85% of the maximum, based on the patient's age. The stress test is considered negative when a patient experiences no episodes of chest discomfort and no change in EKG horizontal or downsloping ST segment with 1 mm depression or greater after reaching the target heart rate. A positive stress test is defined by chest pain and/or ST

segment depression during exercise, suggesting significant myocardial ischemia.

Coronary angiography and ventriculography

Coronary angiography was carried out using the Judkins technique. The right and left coronary arteries were intubated by right and left Judkins 6F catheters. A minimum of two projections of the right coronary artery and four views of the left coronary artery were obtained. The left ventricle angiogram was done in RAO projection for the best visualization of ventricle contraction. The percentage of lesion stenosis in the coronary arteries was evaluated by the computerized quantitative coronary analysis (QCA).

Determination of IgG and IgA antibodies against Chlamydia pneumoniae by enzyme immunoassay (EIA)

Blood samples were taken under basal conditions and the serum subjected to serological analysis. The Cp infection status was assessed by determining the IgG and IgA antibodies against Cp, using a quantitative test, the ImmunoComb Chlamydia Bivalent IgG and IgA Kit (Orgenics Ltd, France). An IgG titer of greater than or equal to 1/32 and an IgA titer of greater than or equal to 1/8 were considered positive.

Determination of plasma interleukin (IL-8) concentration

Plasma IL-8 was measured by an ELISA test using kits supplied by Biosource Europe S.A. (Belgium), and assaying the IL-8 level according to the manufacturer's instructions.

Examination of plasma C-reactive protein (CRP)

C-reactive protein was detected by the latex agglutination test (CRP – Slidex, bioMerieux, France). 50 μl of serum sample was mixed with 50 μl anti-CRP latex reagent. The reaction was considered positive when a distinct agglutination occurred within 3–5 minutes after mixing a serum sample with the anti-CRP latex reagent. The reaction was positive at CRP concentrations of 20–600 mg/l.

Determination of plasma fibrinogen, cholesterol and triglycerides

Plasma fibrinogen was measured by the Clauss thrombin time method (Thrombin Reagent, Baxter, Dade Division, Miami, Florida) with an STA analyzer. The normal range was 1.7 to 3.7 g/L. The inter and intra-assay coefficient of variation was less than 5% for fibrinogen measurements.

The serum concentrations of cholesterol and triglycerides were determined enzymatically by routine laboratory enzymatic methods [24].

Immunofluorescence staining of atheromatous plaques from human coronary artery for confirmation of Cp presence

Arterial samples – plaque fragments from the left arterial descending artery (LAD) – were taken during a direct coronary atherectomy using the Simpson technique [25], and were prepared in the operating theatre under sterile conditions. Two to four specimens were dissected into ca. 2 mm slices and then immersed in liquid nitrogen for further investigation.

For purposes of immunofluorescence, the frozen specimens were cut by cryostat at 5 μm, air-dried and stored in acetone. The slides were then labeled with a C. pneumoniae detection kit (DAKO, K-6601) and reviewed in a laser scanning confocal microscope (OLYMPUS Fluoview) fitted out with argon laser and a filter combination of multi-band path filters for detecting FITS emission. Positive controls were provided by the specimens supplied with the immunodetection kit. Autopsy specimens taken from tissue without atheromatic lesions were used as negative controls. The green apple fluorescence of Cp elementary body was detected and recorded as a computer file in TIFF format.

Statistical analysis

The paired Student t-test was used to assess the differences between groups. With respect to all analyzed variables the level of statistical significance was set at $p<0.05$. The OR test (OR; 95% confidence interval) was used to assess the correlation between the presence of anti-Cp IgG and IgA antibodies and coronary heart disease.

RESULTS

Table 1 shows the number of patients and age distribution of both the CAD and control groups, as well as the percentage of positive results regarding the presence of anti-Cp IgG and IgA and increased levels of IL-8, CRP, fibrinogen, cholesterol and triglycerides. These data demonstrate that both the

Table 1. Evaluated parameters in the CAD and control groups.

	No	Age	IgG anti Cp	IgA anti Cp	CRP [mg/l]	IL-8 [pg/ml]	Fibrinogen [g/l]	Cholesterol [mg/dl]	Triglycerides [mg/dl]
pts with CAD	76	54 (40-68)	46 (60.5%)	47 (61.8%)	20-200	40.5± 3	3.5 ±1.2	241±35	206±24
pts without CAD	81	55 (38-70)	21(26%)	29.5 (29.5%)	7-200	0.9±0.1	2.8±0.9	192±22	170±35
p		NS	<0.001	<0.001	–	<0.001	<0.001	<0.001	<0.001

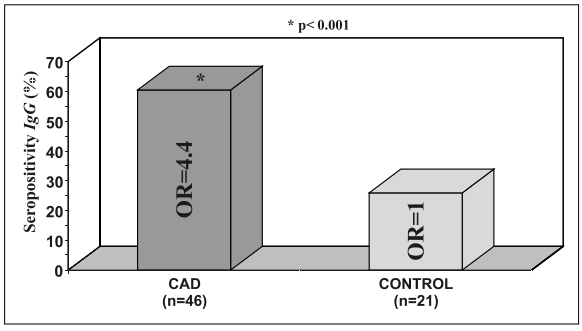

Figure 1. Seropositivity *Chlamydia pneumoniae IgG* and CAD.

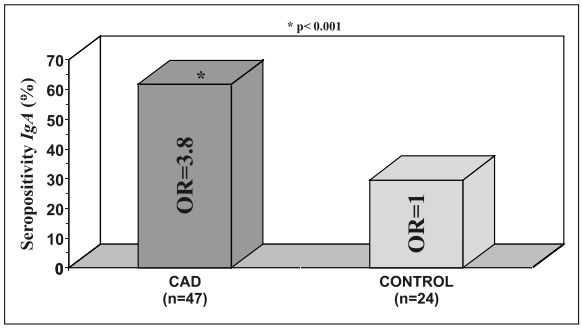

Figure 2. Seropositivity *Chlamydia pneumoniae IgA* and CAD.

CAD patients and the controls were well matched in terms of age, and that there was a significant difference in the overall prevalence of serum IgG and IgA, IL-8, fibrinogen, cholesterol and triglycerides between the CAD patients and the controls.

The presence of Cp infection was significantly higher in Group A patients with CAD than in the healthy controls without CAD (Group B). Seropositivity to Cp was found in 60.5% of the CAD patients for IgG, and in 61.8% for IgA, as opposed to 26.0% and 29.5% respectively among the healthy controls. The odds ratio (OR) in patients with CAD was (IgG; OR=4.4; 95% CI 2.23–8.6; p<0.001) and (IgA; OR=3.8; 95% CI 1.7–8.5 p<0.001) (Fig. 1,2).

IL-8 concentration proved to be positively correlated with CAD. The median plasma levels of IL-8 in patients with CAD was significantly higher than in the controls (40.5 pg/ml vs. 0.9 pg/ml, p<0.001).

The total plasma cholesterol concentration and triglycerides had higher values in patients with CAD than in the controls (241±35 mg/dl for cholesterol and 206±24 mg/dl for triglycerides in the CAD patients, vs. 192±22 mg/dl and 170±35 mg/dl, respectively); the difference between the CAD patients and the controls in these parameters reached a high level of statistical significance (p<0.001).

C-reactive protein (CRP) levels were also higher in patients with CAD compared to the controls (20–200 mg/l vs. 7–200mg/l). This was associated with higher serum fibrinogen in the CAD patients than in the controls (3.5±1.2 g/l vs. 2.8±0.9 g/l). These differences were also highly statistically significant (p<0.001).

The specimens extracted by direct atherectomy from patients diagnosed with severe atherosclerosis in the left descending coronary artery proved to be reactive for chlamydia in direct immunofluorescence. An example of immunofluorescence reactivity to Cp in a case of severe atherosclerosis is shown in Fig. 3.

DISCUSSION

Higher arterial blood pressure, elevated serum cholesterol and smoking are considered the major risk factors in the development of atherosclerosis and coronary heart disease. Furthermore, age, sex, obesity, diabetes, high serum triglyceride count and low high-density lipoprotein (HDL) levels are factors predisposing to CAD. Recent studies have also shown that slightly elevated C-reactive protein (CRP) concentration in serum is a marker of systemic inflammation [26]. Fibrinogen is an acute-phase protein that acts as a cofactor in platelet aggregation. Elevated fibrinogen levels are associated with an increased risk of CAD, due to the effect on platelet aggregation, blood viscosity, vascular permeability and leukocyte chemotaxis.

It is also believed that Cp infections are associated with elevated fibrinogen levels [27]. The concentration of CRP correlates directly with the incidence

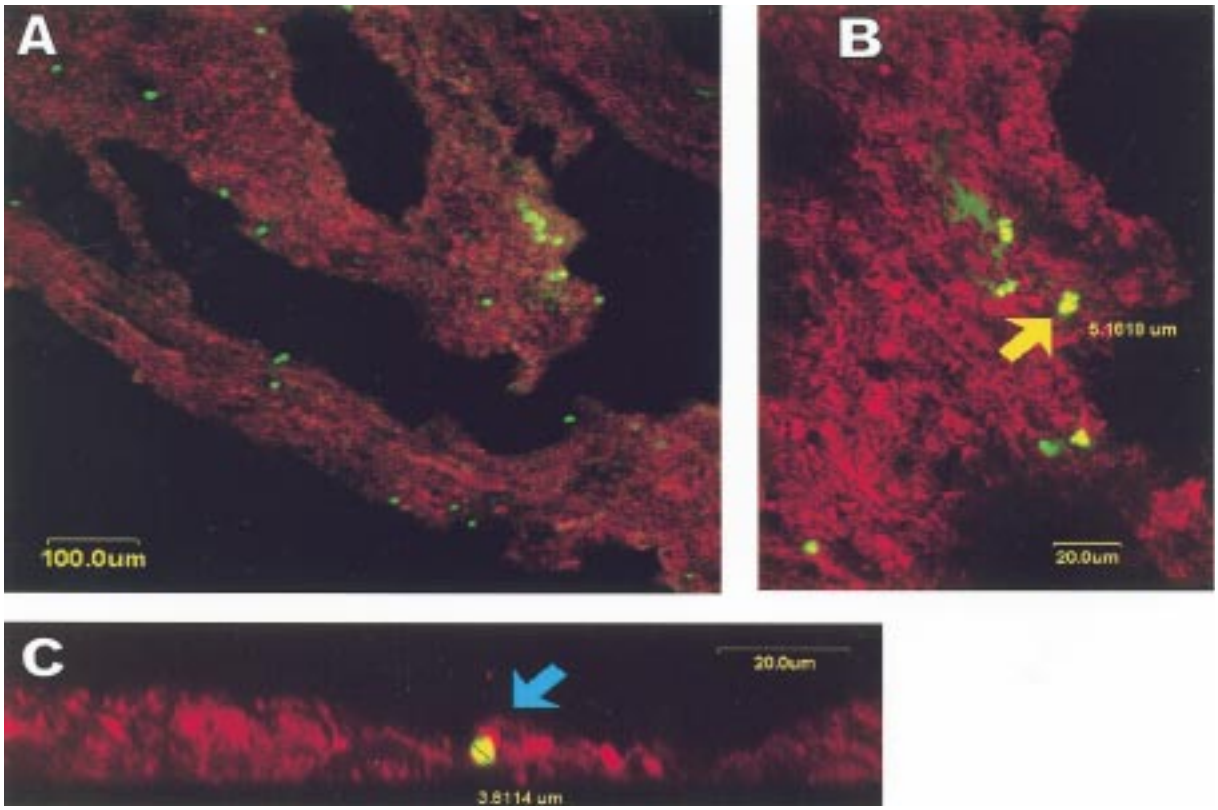

Figure 3. a) Frozen section of coronary atherectomy plaque reacted with antibody FITC-labelled against Chlamydia pneumoniae antigen, as observed using laser confocal scanning microscopy (OLYMPUS Fluoview). A large number of green apple fluorescence staining C. pneumoniae elementary bodies were encountered. b) Higher magnification of Photograph A. The diameter of chlamydial elementary body aggregates in app. 5 μm. c) Cross-section of specimen A. The chlamydial elementary body is located inside the plaque.

and severity of coronary, cerebral and peripheral atherosclerosis. Although CRP may be a useful inflammation marker, its usefulness is by no means limited to artherosclerosis. Cp infection may induce chronic immune activation (mediated by cytokines, such as interleukin 1, 6, 8 and TNF-α) that contributes to direct chronic endothelial cell damage, or stimulates the synthesis of acute phase proteins, such as fibrinogen and C-reactive protein [28–30].

Cytokines that participate in inflammatory reactions [31] are also known to influence lipid metabolism. Tumor necrosis factor-α and IL-1, which are also produced in Cp infections, may inhibit lipoprotein lipase, leading to the mobilization of lipids from tissues and to increased serum triglyceride levels and lower HDL cholesterol concentration. Cp is a gram-negative intracellular bacterium possessing lipopolysaccharides (LPS) as a major constituent of its outer membrane. Its multiplication is associated with cytokine production and the induction of adhesion, although chlamydial LPS has lower endotoxin activity than e. g. enterobacterial LPS [32].

Cp's life cycle causes chronic infection. Chronic infection can lead to elevated levels of CRP, leucocytes and several cytokines; all associated with arteriosclerosis. Several studies have shown that chlamydia germs are encountered in macrophages in a high proportion of atherosclerotic plaques. The production of TNFα and IL-1, IL-6, and other substances may damage the intima and lead to plaque rupture. A variety of techniques, including immunocytochemistry, PCR, electron microscopy and bacterial culture, have been used to confirm the incidence of Cp in human atherosclerotic specimens.

The present study confirmed the incidence of Cp in atherosclerosis lesions by immunofloorescence and laser scanning confocal microscopy. Positive atherectomy specimens were found in young patients with short histories of CAD. Muhlestein et al. [33] detected Cp in 79% of atherectomy specimens, compared with 4% of non-atherosclerotic arteries. The activation of inflammation and a local immune response in the coronary arteries may in some patients be in fact a response to an infection.

The present study showed a high prevalence of Cp infection in patients treated by PCI or CABG. There are very few studies focusing on the follow-up period in patients with Cp infections, treated either by surgery or angioplasty.

Bartels et al. [34] assessed the occluded vein grafts taken from 45 patients subjected to repeat bypass surgery. A strong correlation between elevated IgG titers and the detection of Cp was established. Recently Tiran and associates [35] suggested that the PCI-induced stimulation of the humoral response to Cp after manipulation in atherosclerotic plaques, or in the ascending aorta, may actually be the reason for the elevation of anti-Cp antibodies. Further studies should therefore investigate whether patients undergoing PCI or CABG could profit from antibiotic therapy.

Similar findings regarding strong correlation between Cp IgG and IgA titers and the incidence of coronary heart disease [1,26,33] may be encountered in the literature, although several publications have claimed that there is no evidence for such correlation whatsoever [36–38]. One of the likely causes for such highly contradictory results is that the respective investigators may have used different serologic techniques, and also applied diverse criteria for discriminating between chronic and acute Cp infection.

The measurement of markers of systemic inflammation can be helpful in this strategy. In the present study, IL-8 and fibrinogen were significantly higher in the CAD group, compared to the control group. The slightly elevated CRP in Group A (with atherosclerosis) can only be explained by the common use of aspirin by patients prior to their hospital admission.

Although it has long been commonly acknowledged that serology constitutes an important diagnostic instrument in the assessment of chronic Cp infection, some studies have focused exclusively on assessing IgG or IgA, while others have based their conclusions on either the presence or absence of the circulating immune complex containing Cp LPS. The high prevalence of seropositive cases encountered in the general population probably reflects the incidence of the infection itself and the actual duration of elevated antibody titers following infection. It is therefore difficult to establish whether seropositivity to Cp indicates a chronic, active infection, or simply reflects a past exposure. An accurate diagnosis of active infection would require repeated sampling of serum, with a view toward testing for elevated antibody titters.

The vast majority of the patients we studied had long suffered from stable angina, hence their exposure to Cp infection was in fact quite considerable. It would be both scientifically challenging, as well as of tangible benefit to the patients, to establish whether Cp infection in patients with acute coronary syndrome is a common occurrence, and if so, whether sustained antibiotic therapy could then advantageously impact their long-term prognosis.

CONCLUSIONS

1. The present data confirm the presence of Cp bacteria in the arterial wall using immunocytochemistry.
2. Cp infection significantly increases the risk of coronary artery disease possibly require revascularization.
3. Cp infection seems to modify serum lipids, CRP and fibrinogen levels, which increase the risk of severe coronary atherosclerosis.
4. Our results support the notion that the eradication of Cp may advantageously impact the prognosis for patients with coronary heart disease.

Acknowledgements

The authors would like to express their gratitude to Dr Martin Tewinkel (Olympus Europa) for his expert assistance with the application of laser scanning confocal microscopy.

REFERENCES:

1. *Danesh J, Collins R, Peto R: Chronic infections and coronary heart disease: is there a link? Lancet, 1997; 350: 430-6*
2. *McDonald K, Rector TS, Braunlin EA et al: Association of coronary artery disease in cardiac transplant recipients with cytomegalovirus infection. Am J Cardiol, 1989; 64: 359-62*
3. *Sorlie PD, Adam E, Melnik SL et al: Cytomegalovirus/herpes virus and carotid atherosclerosis: the ARIC study. J Med Virol, 1994; 42: 33-7*
4. *Fabricant CG, Fabricant J, Litrenta MM et al: Virus-induced atherosclerosis. Exp Med, 1978; 148: 335-40*
5. *Patel P, Mendall MA, Carrington D et al: Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. BMJ, 1995; 311: 711-14*
6. *Pieniążek P, Karczewska E, Duda A et al: Association of Helicobacter pylori infection with coronary heart disease. J Physiol Pharmacol, 1999; 50: 743-52*
7. *Kowalski M, Konturek PC, Pieniążek P et al: Prevalence of Helicobacter pylori infection in coronary artery disease and effect of its eradication on coronary lumen reduction after percutaneous coronary angioplasty. Digest Liver Dis, 2001; 33: 222-9.*
8. *Gupta S, Camm AJ: Chlamydia pneumoniae and coronary heart disease: coincidence, association or causation? Br Med J, 1997; 314: 1778-9*

9. *Kuo CC, Shor A, Campell LA et al: Demonstration of chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. J Infect Dis, 1993; 167: 841-9*
10. *Campbell LA, O'Brien ER, Capuccio AL et al: Detection of Chlamydia pneumoniae (TWAR) in human coronary atherectomy tissues. J Infect Dis, 1995; 172: 585-88*
11. *Saikkau P: The epidemiology and significance of Chlamydia pneumoniae. J Infect, 1992; 39: 88-90*
12. *Grayston JT, Wang SP: History of Chlamydia pneumonia (TWAR). In: Allegra L, Blasi F, eds, Chlamydia pneumoniae: the lung and heart. Milan: Springer. 1999: 1-8*
13. *Grayston JT, Kau CC, Wang SP, Altman J: A new Chlamydia psittaci strain (TWAR) isolated in acute respiratory tract infections. N Engl J Med, 1986; 315: 161-8*
14. *Grayston JT: Chlamydia pneumoniae strain (TWAR) pneumonia. Annu Rev Med, 1992; 43: 317-23*
15. *Wong JK, Gallagher PJ, Ward ME: Chlamydia pneumoniae and atherosclerosis. Herat, 1999; 81: 232*
16. *Quaschning T, Wanner H: The role of Chlamydia in coronary heart disease: fact or fiction? Nephrol Dial Transplant, 1999, 14: 2800-2803*
17. *Grayston JT, Wang SP, Kuo CC, Campbell LA: Current knowledge on Chlamydia pneumoniae, strain TWAR, an important cause of pneumonia and other acute respiratory diseases. Eur J Clin Microbiol Infect Dis, 1989; 8: 191-202*
18. *Marrie TJ, Grayston JT, Wang SP, Kno CC: Pneumonia associated with the TWAR strain of Chlamydia. Ann Intern Med, 1987; 106: 507-511*
19. *Kauppinen MT, Herva E, Kujula P et al: The etiology of community-acquired pneumonia among hospitalized patients during a Chlamydia pneumoniae epidemic in Finland. J Infect Dis, 1995; 172: 1330-5*
20. *Saikku P, Mattila K, Nieminen MS et al: Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet, 1988; 2: 983-6*
21. *Shor A, Kuo CC, Patton DL: Detection of Chlamydia pneumoniae in coronary arterial fatty streaks and atheromatous plaques. S Afr Med J, 1992; 82: 158-61*
22. *Kuo CC, Shor A, Campbell LA et al: Demonstration of Chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. J Infect Dis, 1993; 167: 841-9*
23. *Gupta S, Leatham EW: The relation between Chlamydia pneumoniae and atherosclerosis. Heart, 1997; 77: 7-8*
24. *Warnick GR: Enzymatic methods for quantification of lipoprotein lipids. Methods Enzymol, 1886; 129: 101-123*
25. *Topol E: Textbook of Interventional Cardiology, 1990*
26. *Leinonen M: Chlamydia pneumoniae and other risk factors for atherosclerosis. J Infect Dis, 2000; 181 (Suppl 3): S 414-6*
27. *Ernst E: Fibrinogen as a cardiovascular risk factor: interrelationship with infection and inflammation. Eur Heart J, 1993; 343: 1634-5*
28. *Kaukoranta-Tolvanen SS, Teppo AM, Laitinen K et al: Growth of Chlamydia pneumoniae in cultured human peripheral blood mononuclear cells and induction of cytokine response. Microb Pathog, 1996; 21: 215-21*
29. *Patel P, Carrington D, Strachan DP et al: Fibrinogen: a link between chronic infection and coronary heart disease. Lancet, 1994; 343: 1634-5*
30. *Mendall MA, Patel P, Ballam L et al: C reactive protein and its relation to cardiovascular risk factor: a population-based cross sectional study. BMJ, 1996; 312: 1061-5*
31. *Grunfeld C, Feingold KR: Tumor necrosis factor, interleukin and interferon induced changes in lipid metobolism as part of defence. Proc Soc Exp Boil Med, 1992; 200: 224-7*
32. *Ingalls RR, Rice PA, Qureshi N et al: Inflammatory cytokine response to Chlamydia trachomotis is endotoxin mediated. Infect Immun, 1995; 63: 3125-30*
33. *Muhlestein JB, Hammond EH, Carquist JF et al: Increased incidence of Clamydia pneumoniae species within the coronary arteries of patients with symptomatic atherosclerosis versus other forms of cardiovascular disease. J Am Coll Cardiol, 1996; 27: 1555 – 61.*
34. *Bartels C, Maass M, Bein G et al: Association of serology with the endovascular presence of Chlamydia pneumoniae and Cytomegalovirus in coronary artery and vein graft disease. Circulation, 2000; 101: 137-141*
35. *Tiran A, Tio RA, Ossewaarde JM et al: Coronary angioplasty induces rise in Chlamydia pneumoniae-specific antibodies. J Clin Microbiol, 1999; 37: 1013-1017*
36. *Kark JD, Leinonen M, Paltiel O, Saikku P: Chlamydia pneumoniae and acute myocardial infarction in Jerusalem. Int J Epidemiol, 1997; 26: 730-8*
37. *Weiss SM, Roblin PM, Gaydos CA et al: Failure to detect Chlamydia pneumoniae in coronary atheromas of patients undergoing atherectomy. J Infect Dis, 1996; 173: 957-62*
38. *Altman R, Rouvier J, Scazziota A et al: No association between prior infection with Chlamydia pneumoniae and coronary artery disease. Eur Heart, 1998; 1643A [abstract].*